NEU PRESS

SELCUK MEDICAL JOURNAL
SELÇUK TIP DERGİSİ

DOI:http:/dx.doi.org/10.30733/std.2026.01945
Selcuk Med J 2026;42(3): 252-260

OPEN

RESEARCH ARTICLE

Diagnostic Utility of the Corpus Callosum Index in Mild and Moderate Alzheimer's Disease and Its Relationship with Mini Mental State Examination Subcomponents

Hafif ve Orta Evre Alzheimer Hastalığında Korpus Kallozum İndeksinin Tanısal Değeri ve Mini Mental Durum Değerlendirmesi Alt Bileşenleriyle İlişkisi

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ABSTRACT

Objective: This study evaluated the utility of the corpus callosum index (CCI) as a discriminative biomarker between the mild and moderate stages of Alzheimer's disease (AD).

Materials and Methods: A total of 168 individuals were included, comprising two patient groups diagnosed with mild and moderate AD and a control group. CCI values and Mini-Mental State Examination (MMSE) subcomponent scores were compared. Statistical analyses assessed correlations between MMSE subdomains and CCI, group differences, optimal cutoff values using receiver operating characteristic (ROC) analysis, and logistic regression models.

Results: Significant differences in CCI values were observed among the groups ($p < 0.001$). CCI values decreased progressively with increasing dementia severity. A positive correlation was identified between CCI and total MMSE score, as well as orientation, attention-calculation, and language subtests. In the univariate logistic regression analysis, age, CCI, and education level were significant variables; in the multivariate logistic regression model, both CCI and age remained independent predictors of dementia severity ($p < 0.001$ for both). In the ROC analysis, CCI demonstrated high discriminative power between controls and patients with mild dementia (AUC = 0.922) and acceptable discriminative power between mild and moderate dementia (AUC = 0.756).

Conclusion: The findings suggest that CCI may be a useful measure for the early assessment of AD severity. Its high sensitivity in distinguishing controls from patients with mild dementia indicates potential clinical utility as an adjunctive assessment tool. However, larger multicenter prospective studies are needed to draw definitive conclusions regarding the prognostic value and clinical applicability of CCI.

Keywords: Alzheimer's disease, cognitive decline, corpus callosum index, magnetic resonance imaging,mini-mental state examination,

ÖZET

Amaç: Bu çalışma, korpus kallozum indeksinin (KKİ) Alzheimer hastalığının (AH) hafif ve orta evreleri arasında ayırt edici bir biyobelirteç olarak kullanılabilirliğini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler: Hafif ve orta evre AH tanısı alan iki hasta grubu ile bir kontrol grubundan oluşan toplam 168 birey çalışmaya dahil edilmiştir. KKİ değerleri ve Mini-Mental Durum Muayenesi (MMSE) alt bileşen puanları karşılaştırılmıştır. İstatistiksel analizlerde MMSE alt alanları ile KKİ arasındaki korelasyonlar, grup karşılaştırmaları, ROC analizi ile optimal kesim noktaları ve lojistik regresyon modelleri değerlendirilmiştir.

Bulgular: Gruplar arasında KKİ değerlerinde anlamlı farklılıklar saptanmıştır ($p < 0.001$). Demans şiddeti arttıkça KKİ değerleri basamaklı olarak azalmıştır. KKİ ile toplam MMSE puanı arasında pozitif bir korelasyon bulunmuş olup yönelim, dikkat-hesaplama ve dil alt testleri ile ilişkiler gözlenmiştir. Tek değişkenli lojistik regresyon analizinde yaş, KKİ ve eğitim anlamlı bulunmuş; çok değişkenli lojistik regresyon modelinde ise hem KKİ hem de yaş demans şiddetinin bağımsız belirleyicileri olarak kalmıştır (her ikisi için $p < 0.001$). ROC analizinde KKİ, kontroller ile hafif demans arasında yüksek ayırt edicilik (AUC = 0.922) ve hafif ile orta evre demans arasında kabul edilebilir düzeyde ayırt edicilik (AUC = 0.756) göstermiştir.

Sonuç: Bu çalışmanın bulguları, KKİ'nin AH'nin erken evrelerinin değerlendirilmesinde destekleyici bir yapısal ölçüt olabileceğini göstermektedir. Kontroller ile hafif demansı ayırt etmedeki yüksek duyarlılığı, klinik değerlendirmelere potansiyel katkı sağlayabileceğini düşündürmektedir. Ancak KKİ'nin prognostik değeri ve klinik uygulanabilirliği hakkında kesin sonuçlara varılabilmesi için daha geniş örneklemli, çok merkezli prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Alzheimer hastalığı, bilişsel gerileme, korpus kallozum indeksi, manyetik rezonans görüntüleme, mini-mental durum muayenesi

Received: 10 January 2026 **Accepted:** 3 June 2026 **Published Online:** 14 September 2026

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Cite this article as: Sahin O, Kilicaslan Sahin EH. Diagnostic Utility of the Corpus Callosum Index in Mild and Moderate Alzheimer's Disease and Its Relationship with Mini Mental State Examination Subcomponents. Selcuk Med J 2026;42(3): 252-260

Disclosure: *Author has not a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disorder leading to dementia and is characterized in its early stages by memory impairment, particularly affecting episodic memory, deterioration in executive functions, and reduced decision-making ability (1). AD pathology progresses through the accumulation of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles, resulting in neuronal and synaptic loss and consequently widespread brain atrophy (2,3).

The corpus callosum (CC) is the largest white matter structure facilitating information transfer between the right and left hemispheres and plays a critical role in the integrated organization of cognitive functions (1). Regional atrophy, accompanied by demyelination and microstructural alterations in the CC, has been reported in patients with AD (4). Structural changes, particularly in the midanterior and central segments, have been associated with the degree of cognitive impairment and may reflect disease severity (4). The presence of these changes in both AD patients and individuals with mild cognitive impairment (MCI), compared with healthy controls, suggests that the CC may be affected from the early stages of the Alzheimer spectrum (4). Previous studies have reported pronounced changes in shape-based morphometric features of the CC during the early stages of AD, suggesting that these changes may be more sensitive indicators of disease severity and progression than volumetric measurements (5). Structural reductions observed in different CC segments in patients with amnestic MCI and mild AD have also been proposed as early indicators of disease progression (6). In their magnetic resonance imaging (MRI)–based review, Di Paola et al. stated that atrophy in the anterior (genu) segment of the CC is related to myelin degradation in late-myelinating fibers, whereas atrophy in the posterior (splenium) segment is associated with Wallerian degeneration (7). Similarly, morphometric changes in the genu and midbody segments of the CC observed in various neurological disorders have been reported to reflect disruption of transcallosal connections associated with executive functions and attentional networks (8). These findings suggest that segmental morphometric evaluation of the CC may represent a sensitive imaging approach for identifying structural involvement specific to cognitive systems.

In recent years, shape-based morphometric analyses have been more sensitive than conventional volumetric measurements. Ardekani et al. (5) reported that the CC circularity index could discriminate between very mild and mild stages of AD. These findings support the notion that shape- and ratio-based CC measurements may serve as potential biomarkers during the early stages of AD progression. However, heterogeneity in diagnostic criteria and Mini-Mental State Examination (MMSE) cutoff values across Alzheimer's clinical studies limits comparability between disease stages (9). Das et al. (6) demonstrated that CC atrophy is an effective morphometric marker for differentiating patients with mild and moderate AD from healthy individuals. Nevertheless, that study did not include a direct comparison between disease stages and did not specifically focus on distinguishing the Clinical Dementia Rating (CDR) 1 and CDR 2 groups. In this respect, the present study aims to address an important gap in the literature.

The primary aim of this study was to evaluate the potential role of the CC index (CCI) in differentiating disease stages in mild and moderate AD. By examining the extent to which CCI may contribute to clinical classification, we explored whether this structural measurement could serve as a potential biomarker for early diagnosis and follow-up. Additionally, we aimed to analyze the relationships between CCI and MMSE subcomponents (orientation, registration, attention and calculation, recall, and language) to clarify potential associations between cognitive performance and structural changes.

MATERIALS AND METHODS

This retrospective cross-sectional study included individuals aged ≥50 yr who presented to the Neurology Clinic of Aksaray University Training and Research Hospital with complaints of cognitive decline between December 5, 2019, and July 9, 2025. Data were obtained from the hospital's digital archive system. A total of 7,099 patient records were screened, and after duplicate entries were removed, 1,660 unique patient records remained. Among these, 112 patients who met the inclusion and exclusion criteria were enrolled in the study. In addition, 56 healthy controls who fulfilled the imaging and clinical criteria were included, resulting in a total sample of 168 individuals. Demographic characteristics and accompanying comorbidities were recorded for all participants. Eligible individuals were required to have at least a primary school education and sufficient proficiency in Turkish to complete cognitive assessments. Education level was coded in SPSS as a three-level categorical variable (1 = primary school, 2 = middle school, and 3 = high school or higher).

Patients were included if they had an AD diagnosis based on neurological ICD diagnostic codes, complete MMSE and MMSE subcomponent scores in the archive records (orientation, registration, attention and calculation, recall, and language), and cranial MRI obtained at the time of diagnosis. In addition, individuals diagnosed with moderate-stage AD during follow-up who had cranial MRI scans recorded during clinical visits and treatment modifications were also included.

Healthy controls were selected from age-matched individuals who underwent MRI for noncognitive complaints, such as headache or vertigo, and whose imaging findings were reported as normal. The study population was divided into three groups: mild-stage AD (n = 54), moderate-stage AD (n = 58), and healthy controls (n = 56). Because of the retrospective design, individuals with major metabolic or vascular disorders known to substantially affect brain structure, such as poorly controlled diabetes mellitus or uncontrolled hypertension, were excluded from the control group. However, common age-related chronic conditions were not considered exclusion criteria because completely comorbidity-free elderly

individuals are rarely encountered in retrospective cohorts.

Diagnosis and Staging

Alzheimer's disease diagnosis was established according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (9,10). Disease staging was determined through combined evaluation of total MMSE scores, MMSE subcomponent distributions, activities of daily living, treatment protocols, and clinical examination findings. For clinical standardization, staging was matched to Clinical Dementia Rating (CDR) scores of 1 and 2, respectively.

Mild-stage Alzheimer's dementia: Individuals with MMSE scores ranging from 19 to 23, largely preserved functional independence, and clinical findings consistent with CDR = 1 were classified as having mild-stage dementia. In some participants with low educational attainment, an MMSE score of 19 was categorized as mild-stage dementia based on preserved functional independence and concordant clinical evaluation. This approach is consistent with previous reports indicating that the MMSE alone may have limited discriminative capacity (11,12).

Moderate-stage Alzheimer's dementia: Individuals with MMSE scores ranging from 10 to 19 who required substantial assistance with activities of daily living, demonstrated clinical findings compatible with moderate-stage disease, and were managed according to moderate-stage treatment protocols were classified as having moderate-stage dementia, corresponding to CDR = 2.

Inclusion and Exclusion Criteria

Inclusion criteria: Evaluation in the neurology clinic; diagnosis of mild or moderate AD established by a neurology specialist; complete MMSE administration; technically adequate cranial MRI obtained at the time of diagnosis or within 3–4 months after diagnosis; and at least primary school-level education with the ability to complete cognitive tests in Turkish.

Exclusion criteria: History of cranial surgery, cerebrovascular disease, head trauma, neurodevelopmental disorders, psychiatric disorders affecting cognitive function, incomplete clinical records, and causes of dementia other than AD, including vascular dementia.

Corpus Callosum Index Measurement

The CCI was measured on midsagittal T1-weighted MRI sections. CCI was calculated using the following ratio-based formula: (aa'/ab + bb'/ab + cc'/ab) (Figure 1) (13). All measurements were performed twice by a radiologist blinded to the clinical and cognitive data, and the measurements were subsequently confirmed.

Ethical Approval

This retrospective study was approved by the Aksaray University Health Sciences Scientific Research Ethics Committee (Decision No. 2025/173; Meeting Date: 11.09.2025; Protocol No. SAGETIK 2025-114). All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25. The distributional characteristics of continuous variables were assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Comparisons between two nonnormally distributed groups were performed using the Mann–Whitney U test. Variables with three categories that did not show normal distribution were analyzed using the Kruskal–Wallis H test. When significant differences were identified, post hoc multiple comparisons were conducted using Dunn's test with Bonferroni correction. Categorical variables were analyzed using Pearson's chi-square test. Spearman correlation analysis was performed to evaluate the relationships between CCI and age and between CCI and MMSE subcomponents. Binary logistic regression analysis was used to determine the effects of independent variables on discrimination between the mild- and moderate-stage dementia groups. Receiver operating characteristic (ROC) analysis was performed to identify discriminative parameters and determine optimal cutoff values. Continuous variables were presented as median (interquartile range [IQR]) and minimum–maximum values, whereas categorical variables were expressed as number (n) and percentage (%). A two-tailed p value <0.05 was considered statistically significant.

RESULTS

A total of 168 individuals were included in the study, comprising 54 patients with mild dementia, 58 with moderate dementia, and 56 healthy controls. The median age of the entire cohort was 75 yr (IQR: 68–82; range: 51–95 yr). Median age was

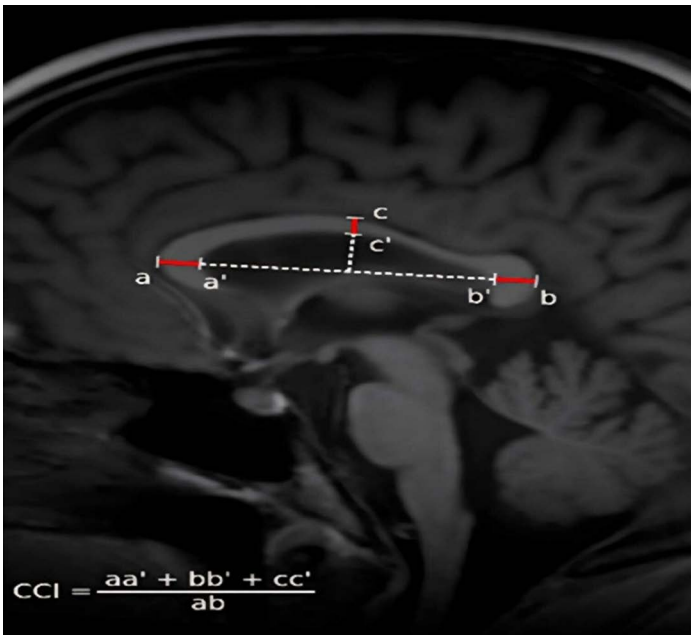

Figure 1. The corpus callosum index (CCI) was measured from midsagittal T1 weighted MRI images and calculated using the ratio of anteroposterior length to segmental heights according to the formula (aa'/ab + bb'/ab + cc'/ab).

72 yr (IQR: 65–80; range: 51–85 yr) in the control group, 75 yr (IQR: 70–80; range: 60–99 yr) in the mild dementia group, and 80 yr (IQR: 75–85; range: 57–95 yr) in the moderate dementia group. Kruskal–Wallis analysis demonstrated a significant difference in age among the groups ($H = 29.753$, $p < 0.001$). Bonferroni-corrected Dunn post hoc analyses indicated that age increased significantly with advancing dementia stage (Table 1).

Among all participants, 72 were male (42.9%), and 96 were female (57.1%). The mild dementia group included 24 males (44.4%) and 30 females (55.6%), whereas the moderate dementia group included 19 males (32.8%) and 39 females (67.2%). In the control group, 29 participants were male (51.8%), and 27 were female (48.2%). No statistically significant difference in sex distribution was observed among the groups ($p = 0.117$). The CCI values differed significantly among the groups (Figure 2). The median CCI was 0.38 (IQR: 0.35–0.41; range: 0.29–0.44) in the control group, 0.29 (IQR: 0.26–0.32; range: 0.16–0.38) in the mild dementia group, and 0.25 (IQR: 0.22–0.28; range: 0.17–0.34) in the moderate dementia group. The median CCI value for the entire cohort was 0.30 (IQR: 0.27–0.35; range: 0.17–0.44). Kruskal–Wallis analysis showed a significant difference in CCI values among the groups ($H = 104.279$, $p < 0.001$). Post hoc analyses demonstrated a progressive decrease in CCI values with increasing dementia severity (Table 1).

Mini-Mental State Examination scores also differed significantly between the dementia groups. The median MMSE score was 20 (IQR: 19–21; range: 19–23) in the mild dementia group and 12 (IQR: 11–14; range: 10–18) in the moderate dementia group. The median MMSE score for the overall dementia cohort was 16 (IQR: 13–19; range: 10–23). Because MMSE is not routinely administered to healthy controls, MMSE subcomponent analyses were performed only between the mild and moderate dementia groups. Patients with mild dementia had significantly higher scores in orientation ($p < 0.001$), attention and calculation ($p < 0.001$), recall ($p < 0.001$), and language ($p < 0.001$) subtests compared with those with moderate dementia. A significant difference was also observed in the registration subtest ($p = 0.007$; Table 2).

Table 1. Comparison of age and CCI values among healthy controls, mild dementia, and moderate dementia groups

Variable	Control (n=56) Median (IQR)	Control Min–Max	Mild Dementia (n=54) Median (IQR)	Mild Min–Max	Moderate Dementia (n=58) Median (IQR)	Moderate Min–Max	Test Statistic (H)*	P
Age (yr)	72 (65–80)[a]	51–85	75 (70–80)[b]	60–99	80 (75–85)[c]	57–95	29.753	<0.001
CCI	0.38 (0.35–0.41)[a]	0.29–0.44	0.29 (0.26–0.32)[b]	0.16–0.38	0.25 (0.22–0.28)[c]	0.17–0.34	104.279	<0.001

a–c: Groups sharing the same letter do not differ significantly from each other, whereas groups with different letters show statistically significant differences (Dunn's test with Bonferroni correction, $p<0.05$). Post-hoc Comparison Explanation (with Test Statistics) Age: Control vs. Mild dementia: Test statistic = 24.225, Std. Test = 2.615, $p = 0.027$. Control vs. Moderate dementia: Test statistic = 49.627, Std. Test = 5.453, $p < 0.001$. Mild vs. Moderate dementia: Test statistic = –25.401, Std. Test = –2.765, $p = 0.017$. CCI: Moderate vs. Mild dementia: Test statistic = 32.205, Std. Test = 3.501, $p = 0.001$. Moderate vs. Control: Test statistic = –91.893, Std. Test = –10.084, $p < 0.001$. Mild vs. Control: Test statistic = –59.688, Std. Test = –6.434, $p < 0.001$. Pairwise comparisons were conducted using Dunn's test with Bonferroni adjustment. CCI: Corpus callosum index; IQR: Interquartile range. * Kruskal–Wallis test statistic.

Comorbidity distributions were evaluated using Pearson's chi-square test. Significant between-group differences were identified for hypertension, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and renal failure (all $p < 0.05$). In contrast, no significant differences were observed for atrial fibrillation, hyperlipidemia, hypothyroidism, or hearing loss (all $p > 0.05$; Table 3). Spearman correlation analysis demonstrated a significant negative correlation between CCI and age ($r = –0.467$, $p < 0.001$), indicating that CCI values decreased with increasing age. A significant positive correlation was observed between CCI and total MMSE score ($r = 0.470$, $p < 0.001$). At the MMSE subcomponent level, significant positive correlations were found between CCI and orientation ($r = 0.391$, $p < 0.001$), attention and calculation ($r = 0.429$, $p < 0.001$), and language scores ($r = 0.357$, $p < 0.001$). However, no significant correlations were identified between CCI and registration ($r = 0.107$, $p = 0.262$) or recall scores ($r = 0.145$, $p = 0.127$).

Logistic regression analysis was performed using mild and moderate dementia groups as dependent variables. The overall model demonstrated a significant fit (Omnibus test: $\chi^2 = 25.324$, $p < 0.001$; Nagelkerke $R^2 = 0.270$), with a classification accuracy of 71.4%. In univariate analyses, age, CCI, and education level were significantly associated with the likelihood of moderate dementia. In the multivariable logistic regression model, age (OR = 1.05, 95% CI, 1.01–1.10; $p = 0.018$) and scaled CCI (OR

Table 2. Comparison of MMSE subcomponents between mild and moderate dementia groups

MMSE Subcomponent	Mild Dementia (n=54) Median (IQR)	Mild Min–Max	Moderate Dementia (n=58) Median (IQR)	Moderate Min–Max	U	P*
Orientation	6 (4–7)	2–9	4 (3–6)	2–8	141.000	<0.001
Registration	3 (3–3)	0–3	3 (3–3)	0–3	1299.000	0.007
Attention & Calculation	1 (0–4)	0–5	0 (0–2)	0–5	147.000	<0.001
Recall	0 (0–1)	0–3	0 (0–0)	0–2	1122.000	<0.001
Language	6 (5–7)	3–7	5 (4–6)	3–7	400.000	<0.001

MMSE: Mini-Mental State Examination; IQR: Interquartile range; Min–Max: Minimum–maximum values. * Mann–Whitney U test

Table 3. Distribution of comorbidities in control, mild, and moderate dementia groups (Pearson Chi-square test results)

Comorbidity	Control (n=56)	Mild (n=54)	Moderate (n=58)	χ^2	p
Hypertension	18 (32.1%)	47 (87.0%)	48 (82.8%)	47.281	<0.001
AF	3 (5.4%)	7 (13.0%)	12 (20.7%)	5.887	0.053
Hyperlipidemia	12 (21.4%)	18 (33.3%)	21 (36.2%)	3.277	0.194
CHF	0 (0%)	6 (11.1%)	9 (15.5%)	8.903	0.012
COPD	2 (3.6%)	12 (22.2%)	16 (27.6%)	12.235	0.002
Hypothyroidism	6 (10.7%)	4 (7.4%)	2 (3.4%)	2.276	0.320
Hearing loss	0 (0%)	5 (9.3%)	4 (6.9%)	5.063	0.080
DM	4 (7.1%)	18 (33.3%)	14 (24.1%)	11.586	0.003
Renal failure	1 (1.8%)	10 (18.5%)	8 (13.8%)	8.218	0.016

Comparisons between the three groups were performed using the Pearson Chi square test. AF: Atrial fibrillation; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus.

Table 4. Univariable and multivariable logistic regression analysis results for distinguishing mild and moderate dementia groups

Variable	Univariate OR (95% CI)	Univariate p	Multivariable OR (95% CI)	Multivariable p
Age (yr)	1.07 (1.02–1.12)	0.010	1.05 (1.01–1.10)	0.018
Sex (male)	0.61 (0.28–1.32)	0.205	0.74 (0.30–1.80)	0.510
Education: Middle school vs primary	1.58 (1.06–2.80)	0.025	1.40 (0.80–2.45)	0.230
Education: High school vs primary	0.58 (0.36–0.94)	0.023	0.62 (0.35–1.10)	0.098
CCI (scaled)	0.98 (0.97–0.99)	<0.001	0.97 (0.95–0.99)	0.004
Hypertension	0.72 (0.25–2.00)	0.530	—	—
AF	1.75 (0.63–4.85)	0.280	—	—
Hyperlipidemia	1.14 (0.50–2.00)	0.750	—	—
CHF	1.47 (0.50–4.30)	0.496	—	—
COPD	1.33 (0.60–2.60)	0.513	—	—
Hypothyroid	0.45 (0.08–2.40)	0.364	—	—
Hearing loss	0.73 (0.18–2.80)	0.647	—	—
DM	0.64 (0.28–1.45)	0.283	—	—
Renal failure	0.70 (0.25–2.00)	0.498	—	—

OR: Odds ratio; CI: Confidence interval; CCI (scaled): Corpus callosum index divided by 1000 for interpretability; AF: Atrial fibrillation; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus. Education was modeled using primary school as the reference category. Variables included in the multivariable model were selected based on clinical relevance and prior literature rather than univariable p-values. Omnibus $\chi^2 = 25.324$, $p < 0.001$; Nagelkerke $R^2 = 0.270$. Note: In logistic regression analysis, the dependent variable was coded as 0 = mild dementia and 1 = moderate dementia.

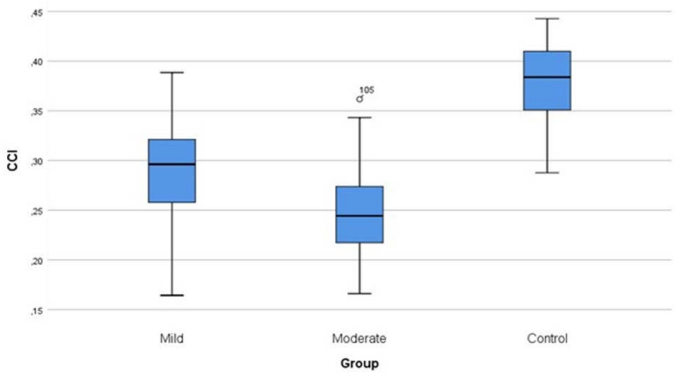

Figure 2. Boxplots showing the distribution of corpus callosum index (CCI) across the control, mild dementia, and moderate dementia groups.

= 0.97, 95% CI, 0.95–0.99; p = 0.004) remained independent predictors of moderate dementia, whereas sex and education level were not significant after adjustment. Other comorbidities were evaluated in univariate analyses but were not included in the multivariable model because they did not reach statistical significance (Table 4).

Receiver operating characteristic analysis demonstrated that CCI had high discriminative ability for differentiating healthy controls from patients with mild dementia (AUC = 0.922, 95% CI, 0.874–0.970). The optimal cutoff value was 0.2886 (sensitivity: 98.2%, specificity: 46.3%, Youden index: 0.445); CCI values below this threshold were more indicative of mild dementia (Figure 3). For discrimination between mild and moderate dementia, CCI showed acceptable discriminative performance (AUC = 0.756, 95% CI, 0.664–0.848). The optimal cutoff value was 0.2446 (sensitivity: 81.5%, specificity: 50.0%, Youden index: 0.315); CCI values below this threshold were more indicative of moderate dementia (Figure 4).

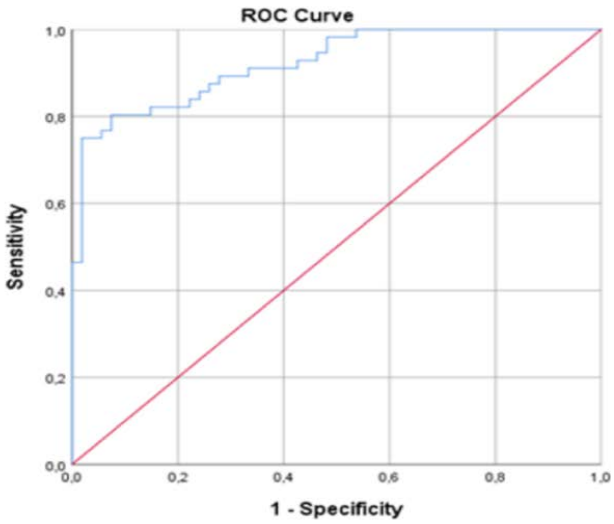

Figure 3. Receiver operating characteristic (ROC) curve of the corpus callosum index (CCI) for distinguishing control and mild dementia groups. The analysis yielded an AUC of 0.922 (95% CI, 0.874–0.970). The optimal cutoff value was 0.2886, with a sensitivity of 98.2%, specificity of 46.3%, and a Youden index of 0.445.

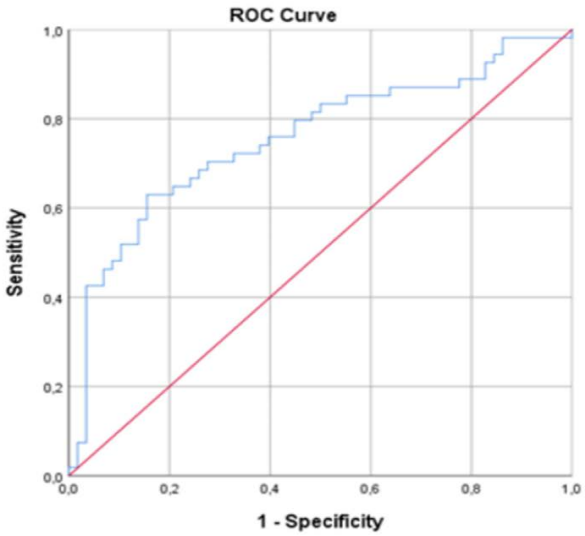

Figure 4. Receiver operating characteristic (ROC) curve of the corpus callosum index (CCI) for distinguishing mild and moderate dementia groups. The analysis yielded an AUC of 0.756 (95% CI, 0.664–0.848). The optimal cutoff value was 0.2446, with a sensitivity of 81.5%, specificity of 50.0%, and a Youden index of 0.315.

DISCUSSION

This study investigated the relationship between the CCI, dementia stages, and MMSE subcomponents and evaluated the potential diagnostic utility of CCI in differentiating mild and moderate dementia. Our findings demonstrated that CCI values decreased progressively with advancing dementia severity and showed particularly high discriminative performance in distinguishing patients with mild dementia from healthy controls. Although increasing dementia severity is known to be associated with advancing age, a significant negative correlation between age and CCI was also observed. This finding suggests that aging may contribute to the structural vulnerability of the CC during the dementia process. In addition, positive correlations between MMSE scores and CCI were most pronounced for the orientation, attention-calculation, and language subtests, indicating a close association between CC structural integrity and cognitive performance.

In logistic regression analyses, age, CCI, and education level were significant in the univariate model. After adjustment for covariates, age and scaled CCI remained independent predictors of moderate dementia, whereas education level and sex were no longer significant. These findings suggest that CCI provides diagnostic value beyond demographic characteristics, while the independent contribution of age is consistent with the established association between aging and dementia severity. Furthermore, reevaluation of the multivariable model confirmed that CCI remained a significant independent predictor even after adjustment for age, indicating that the observed association was not solely attributable to age-related structural alterations.

Receiver operating characteristic analysis demonstrated that CCI had particularly high sensitivity for differentiating healthy controls from patients with mild dementia and acceptable discriminative ability for distinguishing mild from moderate dementia. This high sensitivity suggests that CCI may detect early-stage dementia even when cognitive impairment remains relatively mild. Such structural changes may precede more apparent clinical decline, highlighting the potential role of CCI as an early-stage screening marker. Early identification of mild dementia is clinically important because it may facilitate timely intervention and management planning. However, despite the high sensitivity of CCI in differentiating controls from mild dementia, specificity remained relatively low, indicating a greater likelihood of false-positive classifications in the early stages. Therefore, the clinical applicability of CCI should be considered within a multimodal diagnostic framework rather than as a standalone diagnostic tool. Overall, our findings support the potential utility of CCI as a supportive biomarker in AD. Segmental morphometric alterations reported by Liu et al. (14) and Zhou et al. (8) suggest that different CC regions may exhibit varying sensitivity during disease progression. Consistent with these observations, structural reductions in the genu and midbody regions described in poststroke cognitive impairment studies have been associated with executive dysfunction (8). In the present study, CCI differences reflecting frontal and midbody segments showed significant associations with MMSE subcomponents, particularly attention-calculation and language, supporting the clinical relevance of regional callosal vulnerability. Collectively, the observed relationships between CCI and orientation, attention-calculation, and language functions suggest that callosal structural compromise may clinically manifest as impairments in attentional control, executive processing, and language-related cognitive functions. These findings are consistent with the established role of anterior and midbody callosal fibers in interhemispheric integration of frontal cognitive networks.

The detailed anatomy of the anterior CC and septal region demonstrates dense interhemispheric connections between frontal and limbic cortical areas (15). Recent systematic reviews and meta-analyses have associated this structural organization with executive function, attention, and social cognition (8,16,17). Accordingly, the correlations identified between CCI and orientation and attention subtests may reflect the functional consequences of these anatomical connections. Large-scale systematic reviews and meta-analyses further indicate that morphological changes in the CC are associated with the clinical spectrum and degree of cognitive involvement in AD (16). Wang et al. (18) reported an anterior-to-posterior atrophy pattern, and our findings showing relative preservation of CCI in mild dementia and marked reduction in moderate dementia are consistent with this model. Methodological approaches such as the shape-on-scalar regression model proposed by Dogra et al. (19), which account for confounding factors including age, sex, and education, are also methodologically consistent with our multivariable findings demonstrating that CCI remained an independent predictor. These findings further support the practical utility of CCI as a morphometric marker in clinical settings.

Studies investigating biomarkers have also provided insight into the pathophysiological basis of structural CC changes. Shaji et al. (20) reported that CC abnormalities were associated with phosphorylated tau (p-tau), whereas associations with amyloid-β were less consistent. The limited significant correlations between CCI and memory-related subtests observed in our study may be compatible with this heterogeneous relationship. In addition, multimodal findings summarized by Talwar et al. (21), including hippocampal atrophy, default-mode network hypoconnectivity, and parietal hypometabolism, suggest that CCI may have greater diagnostic utility when evaluated alongside other imaging modalities and biomarkers rather than in isolation. Furthermore, considering the limitations of traditional morphometric indices such as the Evans Index and callosal angle, our findings suggest that CCI may represent a more sensitive and clinically practical metric (14). Overall, our results indicate that CC morphometry provides meaningful information for dementia staging and that CCI may serve as a practical supportive tool in this context. However, the pathological and clinical heterogeneity of AD may limit the generalizability of these findings. Therefore, validation of the prognostic value and multimodal applicability of CCI will require larger prospective studies supported by biomarker integration.

Limitations

This study has several limitations. First, the cross-sectional design precludes definitive conclusions regarding the temporal trajectory of CCI alterations and causal relationships. Therefore, the prognostic utility of CCI can only be confirmed through prospective longitudinal studies. Second, the relatively limited sample size and single-center design may restrict the generalizability of the findings. In addition, because of the retrospective design, MMSE assessments were not available for the control group, limiting objective confirmation of their cognitive status. Third, integration of multimodal imaging and biomarker data was limited. Simultaneous evaluation of CCI together with positron emission tomography, MRS, or cerebrospinal fluid biomarkers would strengthen pathophysiological interpretation of the findings. Fourth, measurement and segmentation procedures may be susceptible to human- or software-related errors.

Finally, the pathological heterogeneity of AD and potential confounding factors, including concomitant vascular changes, may complicate the interpretation of the relationship between CCI and cognitive performance. Although age was adjusted for in multivariable analyses, the marked age differences between groups may still have resulted in residual confounding. Additionally, although CCI measurements were performed twice by the same radiologist, the intraclass correlation coefficient was not calculated, limiting formal assessment of intra-rater reliability.

CONCLUSION

The present study demonstrates that CCI provides meaningful information for dementia staging and has particularly high discriminative ability in distinguishing healthy controls from patients with mild dementia. The consistent associations observed between CCI and MMSE subcomponents further support the relationship between CC morphometry and clinical cognitive function. These findings suggest that CCI may serve as a practical, rapid, and cost-effective morphometric index to complement clinical assessment.

Nevertheless, definitive conclusions regarding the prognostic value and biological specificity of CCI require larger multicenter prospective studies incorporating multimodal imaging and biomarker integration. Future investigations should evaluate CCI across diverse demographic populations, at-risk early-stage groups, and treatment-monitoring settings to further clarify its clinical applicability and utility.

DECLARATIONS

Conflict of Interest: *The authors declare that there is no conflict of interest.*

Financial Disclosure: *The authors report no financial conflicts of interest related to this study.*

Acknowledgements: *We thank Dr. Muhammed Şamil Aydın, Radiology Specialist at Aksaray Training and Research Hospital, for his contributions to the radiological evaluation of this work.*

Funding: *No financial support was received for this study.*

Author Contributions: *Concept: O.Ş., E.H.K.Ş. Design: O.Ş., E.H.K.Ş. Data Collection or Processing: O.Ş. Analysis or Interpretation: O.Ş., E.H.K.Ş. Literature Search: O.Ş., E.H.K.Ş. Writing: O.Ş., E.H.K.Ş.*

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